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10/567,536	01/03/2007	Tim Hitchman	564462012600	9324

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VERENIUM C/O MOFO S.D.
12531 HIGH BLUFF DRIVE
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SAN DIEGO, CA 92130-2040

EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,536	HITCHMAN ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5* is/are allowed.

6)☒ Claim(s) *1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271* is/are rejected.

7)☒ Claim(s) *266* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-6,10,11,13,21-23,27,31,34,36-38,40-42,45,47,106,126,128,151,167,197 and 259-271.

Application Status

In response to the Non-Final Office Action dated 02/12/09, applicants' response filed on 05/12/09 is acknowledged. In said response, applicants' amended claims 1-3, 5, 6, 10, 22, 23, 27, 42, 45, 47 and 267-269 and cancelled claims 7, 24, 25 and 272.

Claims 1-6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197and 259-271 are pending, and are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby

Withdrawn-Claim Rejections: 35 USC § 112, first paragraph

Previous rejection of claim 45 (directed to a transformed cell comprising the nucleic acid of claim 1) rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because, while claim 45 is enabling for an isolated host cell transformed with the synthetic nucleic acid as claimed, does not reasonably provide enablement for transgenic multi-cellular organisms or host cells within a multi-cellular organism that have been transformed with the synthetic nucleic acid, is being withdrawn due to amendments to claim.

Claim Objections

Claim 6 is objected to under 37 CFR 1.75(c) as being in improper form, because a multiple dependent claim shall not serve as a basis for any other multiple dependent claim. Claim 6 depends on claims 1 through 5 which are multiple dependent claims and depending from dependent claim 4. See MPEP § 608.01(n). Accordingly, the claim 6 has not been further treated on the merits.

Claims 22 and 23 are objected to because of the following informality:

Applicant is advised that should claim 22 be found allowable, claim 23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 23 is similar in scope to claim 22. Appropriate correction is required.

Maintained-Claim Rejections: 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for an isolated polynucleotide of SEQ ID NO: 23 encoding a polypeptide of SEQ ID NO: 24 having laccase and comprising peroxidase activity, vectors, isolated host cells comprising the polynucleotide and methods for making and using said polypeptide, does not reasonably provide enablement for any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45

and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 are so broad as to encompass any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides and encoded polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein

encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to an isolated polynucleotide of SEQ ID NO: 23 encoding a polypeptide of SEQ ID NO: 24 having laccase activity, vectors, isolated host cells comprising the polynucleotide and methods for making and using said polypeptide. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides and encoding polypeptides that are having at least at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities and said polynucleotides encoding a polypeptide having laccase and peroxidase activities. The specification is limited to teaching the use of a polynucleotide sequence of SEQ ID NO: 23 encoding a polypeptide having laccase and peroxidase activities, but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make and use the claimed polynucleotides and encoded polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary

structure (for example, see Whisstock et al., Prediction of protein function from protein sequence and structure. Q Rev Biophys. 2003, Aug. 36 (3): 307-340. Review), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polynucleotides and polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

Claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 as written are directed to random variant and mutant polypeptides having laccase and peroxidase activities and encoded by random mutants and variants of a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 23 i.e., any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells

comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271) as this correlates to ~ 67-127 nucleotide residues at either the 5' or 3' end of the polynucleotide sequence of SEQ ID NO: 23 is completely undefined structurally and said polynucleotide encoding a polypeptide having laccase and peroxidase activities (Full-length polynucleotide sequence of SEQ ID NO: 23 comprises 1767 nucleotide residues). The guidance provided by the applicants is limited and especially to an isolated polynucleotide of SEQ ID NO: 23 encoding a polypeptide of SEQ ID NO: 24 having laccase activity, vectors, isolated host cells comprising the polynucleotide and methods for making and using said polypeptide. However, polynucleotides having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities, said polynucleotides encoding random variant and mutant polypeptides having laccase and peroxidase activities would clearly constitute **undue** experimentation. Furthermore, there is paucity of information in prior art that teaches laccase structures defining the catalytic domains, crystal structures and 3D model of a laccase and additionally having peroxidase activity. Therefore, enough guidance is not presented to the skilled artisan that enables the skilled artisan to identify amino acid residues that are amenable to changes and to identify variant structures of SEQ ID NO: 23 and encoding polypeptide with the associated laccase and peroxidase function. Therefore, polynucleotides having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID

NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities, said polynucleotides encoding random variant and mutant polypeptides having laccase and peroxidase activities, method of making and method of using said encoded polypeptides would clearly constitute **undue** experimentation (see scientific support below).

Guo et al., (PNAS, 2004, Vol. 101 (25): 9205-9210) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (p 9206, paragraph 4). Guo et al., (*supra*) further show that the percentage of active mutants for multiple mutations/changes appears to be exponentially related to this by the simple formula $(0.66)^{x}$ X 100% where **x** is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, i.e., ~ 67-127 nucleotide residues at either the 5' or 3' end of the polynucleotide sequence of SEQ ID NO: 23 is completely undefined structurally and said polynucleotide encoding a polypeptide having laccase and peroxidase activities (Full-length polynucleotide sequence of SEQ ID NO: 23 comprises 1767 nucleotide residues); the estimated number of finding an active mutant from among enormously high number of inactive mutants is as follows: $(0.66)^{127}$ – $(0.66)^{67}$ X 100% or **1.2×10^{-21}% - 8.1×10^{-11}%** of mutants having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues, said polynucleotides encoding random variant and mutant polypeptides would be active. While these calculations are only estimates

of the actual situation, they are presented to provide a basis for understanding the examiner's decision on which claim scope would require only routine experimentation and which claim scope would reach a level which is undue. The guidance in the instant case and current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a reasonable number of active mutants within hundred thousand inactive mutants of SEQ ID NO: 23. But finding a few mutants within several billions to trillions or more, as in the claims to at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (guided mutants). Such guidance has **not** been provided in the instant specification.

It is also noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry, 1999, Vol. 38: 11643-116150) teaches that one conservative amino acid substitution transforms a $\tilde{\beta}$-ketoacyl synthase into a malonyl decarboxylase and completely eliminates $\tilde{\beta}$-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol., 2001, Vol. 183 (8): 2405-2410) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function.

The specification does not support the broad scope of the claims which encompass 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 as written are directed to random variant and mutant polypeptides having laccase and peroxidase activities and encoded by random mutants and variants of a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 23 i.e., any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271), because the specification does not establish: (A) a rational and predictable scheme for modifying specific nucleotides in the polynucleotide sequence of SEQ ID NO: 23 encoding a polypeptide having laccase and peroxidase activities; (B) a rational and predictable scheme for modifying any nucleic acid residue or an amino acid residue in the encoded polypeptide with an expectation of obtaining the desired biological function; (C) the tertiary structure of the molecule and folding patterns that are essential for the desired biological activity and tolerance to modifications; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides and polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1975)). Without sufficient guidance, determination of polynucleotides and polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the prior rejection of claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 under 35 U.S.C. 112 for enablement be withdrawn, applicants', provide the following argument.

"The instant amendment addresses this issue. For example claim 1 has been amended to encompass polynucleotide comprising 95% sequence identity to SEQ ID NO: 23, over at least 1650 nucleotides, encoding polypeptides having laccase activity. Accordingly, the specification has been amended enables a person of ordinary skill in the art to make and use the invention as claimed, without undue experimentation" (page 12 of applicants' response dated 05/12/09).

Reply: Applicants have construed that claim amendments have adequately addressed the issue of enablement rejection, however as noted by

the examiner, the scope of the claims are broad despite the amendments, guidance of the art and the guidance in specification, the claims remain not commensurate in scope with the enabled invention; i.e.,

A) any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271) as this correlates to ~ 67-127 nucleotide residues at either the 5' or 3' end of the polynucleotide sequence of SEQ ID NO: 23 is completely undefined structurally and said polynucleotide encoding a polypeptide having laccase and peroxidase activities (Full-length polynucleotide sequence of SEQ ID NO: 23 comprises 1767 nucleotide residues).

B) there is paucity of information in prior art that teaches laccase structures defining the catalytic domains, crystal structures and 3D model of a laccase and additionally having peroxidase activity. Therefore, enough guidance is not presented to the skilled artisan that enables the skilled artisan to identify amino acid residues that are amenable to changes and to identify variant structures of SEQ ID NO: 23 and encoding polypeptide with the associated laccase and peroxidase function.

C) Furthermore, the following claims as written are also not enabled:

i) Claim 27 and claim 128 depending therefrom, as written is interpreted to recite "anything comprising any 60 to 150 nucleotides of SEQ ID NO: 23 or anything 95% identical to any 60 to 150 nucleotides of SEQ ID NO: 23 and hence lacks structure correlated to function. In addition claim 27 fails to recite the hybridization conditions and hence the scope of the claim is not clear.

ii) In claim 31 and claim 126 depending therefrom, the primers as recited will not amplify SEQ ID NO: 23 and therefore not enabled, as a forward and a reverse primer are required for amplification. The second primer must comprise at least 12 nucleotides of the reverse complement.

iii) Claims 34, 36 and 37 that depend from claim 31 are also not enabled as they do not recite any structure correlated to function.

Examiner further suggests the following amendments:

Claim 10: Line 2, insert "encoded polypeptide having" after "wherein the"

Claim 11: Line 2, insert "encoded polypeptide having" after "wherein the"

Claim 13: Line 2, insert "encoded polypeptide having" after "wherein the"

Claim 21: Line 2, insert "encoded polypeptide having" after "wherein the"

Claim 22: Line 2, delete "wherein the polypeptide retains a" and replace with "wherein the encoded polypeptide retains the"

Claim 31: Line 2, delete "having a" and replace with "having"

Lines 4 and 5 delete "bases" and replace with "nucleotides"

Claim 106: Line 1, delete "having a" and replace with "having"

Claim 126: Line 2, delete "with a" and replace with "with" and

Line 9, delete "with a" and replace with "with"

Claim 128: Line 2, delete "with a" and replace with "with" and

Line 9, delete "with a" and replace with "with"

Claim 151: delete lines 6 and 7 and replace with "conditions that facilitate oxidizing the aromatic amine by the laccase enzymatic reaction."

Examiner additionally finds support for his position in the following scientific teachings:

D) As taught by the art, even highly structurally homologous polypeptides do not necessarily share the same function and many functionally similar proteins will have little or no structural homology to disclosed proteins. For example, proteins having similar structure have different activities (structure does not always correlate to function); Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have same function but different structures.

Therefore, examiner takes the position that due to the paucity of information regarding structure-function correlation, the specification lacks identifying characteristics of all of the sequences within the claimed genus, especially; any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271).

The broadest interpretation of claims encompass a genus of polynucleotides, encoding polypeptides and their variants with any structure having the associated function of laccase and peroxidase activities and clearly constitutes undue experimentation, as it would involve making and testing many variant sequences.

Claims are given the broadest interpretation and under this interpretation when there are no defined structural features, the modified/variant polypeptide having laccase and peroxidase activities can potentially have any number of structural features with no correlation to structure-function.

The specification fails to enable the skilled artisan to know which of the large number of possible mutants, variants and recombinants have the desired characteristics. Moreover, it would be undue experimentation for a skilled artisan, as the skilled artisan would be required to make and test an essentially unlimited

number of corresponding mutants, variants and recombinants. Examiner would like to reiterate that to determine the effect of structural modification on any polypeptide having laccase and peroxidase activities, a skilled artisan should be provided with details and guidance regarding the how the structure of any polypeptide having laccase and peroxidase or a variant thereof is correlated with its activity. Given this structural complexity, the specification is limited to the guidance provided i.e., an isolated polynucleotide of SEQ ID NO: 23 encoding a polypeptide of SEQ ID NO: 24 having laccase and comprising peroxidase activity, vectors, isolated host cells comprising the polynucleotide and methods for making and using said polypeptide.

For these reasons, claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 are rejected under 35 U.S.C. 112, first paragraph for enablement as the scope and breadth of the claims encompasses many polypeptides with different structures lacking correlated function and hence, the guidance provided by the art or the specification is in-sufficient, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Written Description

Claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271, as interpreted, are directed to a genus of nucleic acids wherein said nucleic acids encompass a large number of variant polynucleotides encoding polypeptides; i.e., any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271).

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, there is no structure associated with functional limitations recited with regard to the members of the genus of polynucleotides encompassing a large number of variant polynucleotides and encoding polypeptides; i.e., any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271).

A sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by their nucleotide sequence or a recitation of structure-function correlated features common to members of the genus, which features constitute a substantial portion of the genus. While the specification in the instant application discloses the structure of an isolated polynucleotide of SEQ ID NO: 23 encoding a polypeptide of SEQ ID NO: 24 having laccase activity, vectors, isolated host cells comprising the polynucleotide and methods for making and using said polypeptide and said polynucleotide (SEQ ID NO: 23) is not representative of the structure and function of all members of the claimed genus. The specification fails to disclose by any relevant, identifying characteristics or functional properties of all the

members of the genus i.e., any information as to the structures associated with functions.

The genus of polynucleotides and encoding polypeptides required in the claimed invention is an extremely large structurally and functionally variable genus i.e., any isolated polynucleotide having at least 95%-99% sequence identity with an isolated polynucleotide of SEQ ID NO: 23 over a region of 1650-1700 residues and encoding a polypeptide having laccase and peroxidase activities (as in claims 1-4, 6, 7, 10, 11, 13, 21, 22-25, 27, 31, 34, 36-38, 197, 267, 268 and 269), vectors (as in claims 40-42), host cells comprising said polynucleotides (as in claims 45 and 47) and methods for making and using said polypeptide (as in claims 106, 126, 128, 151, 167, 259-265, 270 and 271) as this correlates to ~ 67-127 nucleotide residues at either the 5' or 3' end of the polynucleotide sequence of SEQ ID NO: 23 is completely undefined structurally and said polynucleotide encoding a polypeptide having laccase and peroxidase activities (Full-length polynucleotide sequence of SEQ ID NO: 23 comprises 1767 nucleotide residues).

While the argument can be made that the recited genus of polynucleotides is adequately described by the disclosure of the structure of an isolated polynucleotide of SEQ ID NO: 23 encoding a polypeptide having laccase activity, since one could use structural homology to isolate those polynucleotide and encoding polypeptides recited in the claims. As taught by the art, even highly structurally homologous polynucleotides and encoded polypeptides do not necessarily share the same function. For example, Witkowski et al.,

(Biochemistry 38:11643-11650, 1999), teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β̃-ketoacyl synthase activity. Seffernick et al., (J. Bacteriol. 183(8): 2405-2410, 2001), teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, the claimed genera of polynucleotides include encoding polypeptides having widely variable structure and associated functions, since minor changes in structure may result in changes affecting function and no additional information correlating structure with several distinct functions has been provided.

Due to the fact that the specification only discloses an isolated polynucleotide of SEQ ID NO: 23 encoding a polypeptide having a laccase activity and the lack of description of any additional species/variants/mutants/recombinants by any relevant, identifying characteristics or properties or structure-function correlationship for the cited distinct functions/activities, one of skill in the art would not recognize from the disclosure that applicant was in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In support of their request that the prior rejection of claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 under 35 U.S.C. 112 for written description be withdrawn, applicants' have provided a common line of argument for traversing enablement and written description.

"The instant amendment and the reason stated above address this issue. Additionally, all of the species within the amended genus share a significant degree of partial structure…" (page 12 of applicants' response dated 05/12/09).

Reply: Examiner's answer, rebutting the applicants' argument for maintaining the enablement rejection applies equally in maintaining the written description rejection. Examiner continues to hold the position that, the genus of polynucleotides and encoded polypeptides as recited in the claimed invention is an extremely large and structurally variable genus. Therefore, the claimed genera of polynucleotides and encoded polypeptides include polynucleotides and encoded polypeptides having widely variable structures, since minor structural changes may result in changes affecting function and no additional information correlating structure with function has been provided.

Many structurally unrelated polynucleotides and encoded polypeptides are encompassed by these claims. The specification only discloses a single species within the recited genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the

applicant had possession of the claimed invention at the time the instant application was filed.

As argued by the examiner above in the enablement rejection, the genus of polynucleotides ane encoded polypeptides required in the claimed method/invention is extremely large and structurally variable genus. Therefore, claims as written lack structure-function correlationship, structure correlated with function is necessary, as supported by scientific evidence that even minor changes in structure may result in drastic changes in function. As taught by the art, even highly structurally homologous polypeptides do not necessarily share the same function and many functionally similar proteins will have little or no structural homology to disclosed proteins. For example, Witkowski et al., (Biochemistry 38:11643-11650, 1999), teaches that one conservative amino acid substitution transforms a β̃-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β̃-ketoacyl synthase activity. Seffernick et al., (J. Bacteriol., 183(8):2405-2410, 2001), teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase.

Therefore, the claimed genera of polynucleotides and encoded polypeptides include proteins having widely variable structures, since minor structural changes may result in changes affecting function and no additional

information correlating structure with function has been provided. Thus, the instant claims would encompass many different structures with no correlation to associated functions, in the absence of such information further testing of the variants and mutants would be required by the skilled artisan. Based on the lack of knowledge and predictability in the art (see scientific evidence above), amended claims as written would encompass polynucleotides and encoding polypeptides that are structurally divergent with concomitant change in the function. For these reasons, claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 are rejected under 35 U.S.C. 112, first paragraph for written description.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197, 259-265 and 267-271 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and enablement.

2. Claim 266 is objected as said claim depends from rejected base claim, claim 6.

3. Claim 5 is allowable.

Conclusion

Claims 1-4, 6, 10, 11, 13, 21-23, 27, 31, 34, 36-38, 40-42, 45, 47, 106, 126, 128, 151, 167, 197 and 259-271 are objected/rejected for the reasons identified in the Rejections and Summary sections of this Office Action.

Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ganapathirama Raghu/
Patent Examiner
Art Unit 1652.